IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Kathleen C.M. Campbell Art Unit 1614
Serial No. 10/694,436
Filed October 27, 2003
Confirmation No. 8942
For THERAPEUTIC USE OF METHIONINE TO FOR THE TREATMENT OR PREVENTION OF MUCOSITIS
Examiner Shirley V. Gembeh

DECLARATION OF PRASAD SUNKARA UNDER 37 CFR 1.132

I, Prasad Sunkara, hereby declare and state as follows:

1. I received a Ph.D in Biochemistry from the Indian Institute of Science, Bangalore, India. After completing a post doctoral fellowship in Cell Biology, I joined the faculty at M.D. Anderson Cancer Center in Houston, Texas, as an Assistant Professor of Cell Biology. I was employed at Marion Merrell Dow Research Institute in Cincinnati for 13 years and ended my time there as the Head of Tumor Biology wherein I was responsible for research and preclinical development of cancer and antiviral therapeutics. In all, I have more than 27 years of research and development management experience in cancer therapeutics at major pharmaceutical and biotech companies.

2. I am currently Chairman and Chief Executive Officer of Molecular Therapeutics, Inc.

3. Under my direction and control, pharmaceutical formulations containing D-methionine (MRX-1024, an oral formulation of D-methionine) were evaluated as agents to reduce mucositis arising as a side effect of standard treatment of head and neck cancer. Patients were treated with radiation alone or radiation combined with cisplatin chemotherapy.

4. On the basis of the attached Phase 1 study, the following findings were made.

A. MRX-1024 is a well-tolerated agent when given orally at a dose of 100 mg/kg twice a day to patients with head and neck cancer receiving standard therapy with radiation or radiation plus cisplatin chemotherapy.

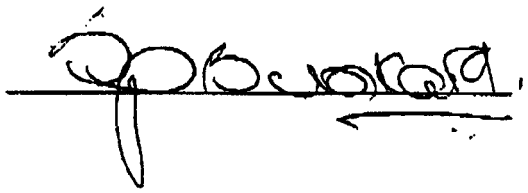
B. When compared to historical control data, MRX-1024 provides a substantial protective effect against development of oral mucositis, a common and severe consequence of radiation or radiation plus cisplatin chemotherapy, in patients with head and neck cancer.

C. Antitumor activity is preserved when MRX-1024 is co-administered with radiation or radiation plus cisplatin chemotherapy to patients with head and neck cancer.

D. Additional clinical trials are warranted in patients with head and neck cancer receiving standard therapy to further evaluate the contribution of MRX-1024 in reducing the incidence and severity of oral mucositis.

5. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the Unites States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: 7-17-06



Protocol Number MRX-1024-A-01

Phase 1b Pilot Open-Label Study to Evaluate the Safety and Efficacy of MRX-1024 Given Orally to Reduce the Severity and Duration of Mucosal Injury Associated with Radiation Treatment in Patients with Head & Neck Cancer

Final Report

Study Site:
Department of Clinical Pharmacology and Therapeutics
Department of Radiation Oncology
Nizam's Institute of Medical Sciences
Hyderabad, India

Investigators

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Dr. S. Venkatratnam
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Sponsored By

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SYNOPSIS

Title of Study: Phase 1b pilot open-label study to evaluate the safety and efficacy of MRX-1024 given orally to reduce the severity and duration of mucosal injury associated with radiation treatment in patients with head and neck cancer.

Investigators: M. U. R. Naidu, S. Venkatratnam, P. U. Rani, J. R. Naidu, S. Vani, I. K. Mohan, G. V. Ramana

Study Center: Department of Clinical Pharmacology and Therapeutics, Department of Radiation Oncology, Nizam's Institute of Medical Sciences, Hyderabad, India

Objectives: The objective of this Phase 1 study was to evaluate oral MRX-1024 in patients with head and neck cancer who were receiving radiation alone or radiation plus chemotherapy. Endpoints of the study included describing the safety of MRX-1024 and the incidence and severity of oral mucositis resulting from concomitant radiation or radiation plus chemotherapy.

Methodology: Open-label, multiple-dose, single-center, Phase 1 study in patients with head and neck cancer.

Number of Patients: Twenty-five patients were enrolled. This is a final report summarizing data reported from all 25 patients.

Diagnosis and Major Criteria for Inclusion: Adults with head and neck cancer who were to receive radiation alone or radiation combined with cisplatin chemotherapy. Additional eligibility criteria included Karnofsky Performance Score $\geq$60 and adequate liver, renal, and bone marrow function, as defined in the protocol.

Test Product, Dose, Method of Administration: MRX-1024 was given twice daily as an oral suspension, one hour before and 15 minutes after each dose fraction of radiation. Doses used included 25 mg/kg and 100 mg/kg.

Treatment Administered: In addition to treatment with MRX-1024, patients received 1.8 to 2.0 Gy of radiation daily for 5 consecutive days each week, until a total dose of 60 Gy was delivered. Patients selected by the investigator also received cisplatin, $50mg/m^2$ once a week.

Safety Evaluations: Patients were examined by the investigator during each Study Visit. Adverse events were documented in the Case Report Forms.

Efficacy Evaluations: The investigator examined the oral cavity of each patient at baseline and at each Study Visit for the presence of oral mucositis. Any such evidence, or lack thereof, was reported on the Case Report Forms using standardized toxicity rating scales.

Preliminary Findings: MRX-1024 appears to be a well-tolerated agent when co-administered with radiation or radiation plus cisplatin chemotherapy to patients with head and neck cancer. MRX-1024 appears to substantially reduce the incidence and severity of oral mucositis that is customarily associated with such standard therapy. MRX-1024 does not appear to compromise the antitumor effect of such standard therapy.

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1. INTRODUCTION

Chemotherapy and radiation are the most widely used modalities for treating advanced cancer. Adverse reactions caused by these therapies may result in increased patient morbidity, compromised therapy, additional economic impact of the disease, and infrequently death. Oral complications that arise with radiation or with the combination of radiation with chemotherapy include mucositis, xerostomia, infection, dental caries, loss of taste, and osteoradionecrosis. Oral mucositis is a painful, debilitating, and dose-limiting adverse reaction of both radiation and chemotherapy in which the oral mucosa undergoes apoptosis and develops ulcers, often with secondary bacterial or fungal infections. These ulcers put the patient at a increased risk of developing septicemia. Oral mucositis is frequently associated with significant morbidity including pain, difficulty chewing and swallowing, loss of taste, and when severe may result in dehydration, malnutrition, and weight loss. These complications frequently require interruption of planned therapy, possibly compromising the intended effects of treatment. Aside from direct morbidity, oral mucositis contributes indirectly to increased length of hospitalization and increased cost of treatment.[1] With the improved ability to manage other treatment-related adverse reactions such as myelosuppression, oral mucositis has become one of the major dose-limiting toxicities of cancer therapy. As there are no effective therapies available for the prevention or treatment of oral mucositis, this complication represents a very large and unmet medical need. Many agents have been studied, but for most positive confirmatory studies are lacking.[2]

The probability of developing mucositis from radiation is related to the radiation source, cumulative dose, dose intensity, the volume of radiated mucosa, smoking, alcohol consumption and oral hygiene. The probability of developing mucositis from chemotherapy is related to the agents used, method of administration, dose intensity, number of cycles administered and previous episodes of mucositis. Approximately 30 to 60% of head and neck cancer patients receiving radiation alone, and greater than 90% of such patients receiving radiation plus chemotherapy, develop mucositis.[3] Most of these cases are rated as Grade 3, defined according to standardized toxicity grading scales by

the presence of painful erythema, edema, or ulcers that preclude eating, or Grade 4, cases requiring parenteral or enteral nutritional support. Because these symptoms commonly arise during the intended treatment course, standard practice calls for the use of a 'treatment holiday', allowing the patient to recover before completing the planned treatment. Approximately 50% of patients receiving radiation and/or chemotherapy develop severe dose-limiting oral mucositis necessitating a treatment holiday, thereby compromising prognosis.[4]

The study center that conducted the herein reported Phase 1 study established a historical control database consisting of 33 patients with head and neck cancer who were treated with the same radiation and chemotherapy regimen as used in the current study. These patients were treated over an interval (February 2003 through December 2003) that immediately preceded the study period. In addition to receiving the same treatment regimen, these patients were evaluated by the same clinicians using the same grading scale used in the Phase 1 study. Thirteen patients received radiation alone. Nine of these patients (69%) developed oral mucositis of at least Grade 2 severity, as follows: Grade 2 (2 patients), Grade 3 (4 patients) and Grade 4 (3 patients). Twenty patients received radiation plus chemotherapy (cisplatin). Nineteen of these patients (95%) developed oral mucositis of at least Grade 2 severity, as follows: Grade 2 (3 patients), Grade 3 (12 patients) and Grade 4 (4 patients). Overall, 28 of 33 patients (85%) developed oral mucositis, 23 of them (70%) having Grade 3 or 4 severity.

It is well-understood that radiation-induced mucositis is due to the oxidative stress on the oral mucosa. MRX-1024, the dextro isomer of the essential amino acid L-methionine, is a small molecule that has free radical scavenging activity.[5] The compound is also known to increase mitochondrial glutathione (GSH), an effect that can prevent oxidative stress-induced apoptosis.[6,7] MRX-1024 showed significant protection of radiation and chemotherapy-induced cytotoxicity to normal cells while providing no such protection to tumor cells, both in cell cultures and in animal tumor models. The compound prevented radiation-induced oral mucositis in a mouse model without interfering with the antitumor activity of chemoradiation treatments.

MRX-1024 is a compound known to have relatively low toxicity.[8,9] It is used throughout Europe and India in high doses (total dose of 10 g given over 12 hours) to prevent toxicities associated with acetaminophen overdose.[10] It is also used in lower doses (200-400 mg 3 to 4 times a day) to reduce urinary odor and dermatitis.[11,12,13] The D-isomer appears to be better tolerated than either the L-isomer or the racemic mixture.[14,15] In the human, D-methionine results in higher plasma levels than L-methionine, which could be advantageous for a protective agent. D-methionine has adequate bioavailability and a longer half-life than L-methionine.[16] Studies suggest that D-methionine itself is not toxic unless converted to the L-isomer.[14,15,17-19]

Based on encouraging preclinical data and the expected safety of the compound, we initiated a Phase 1 study of MRX-1024 in patients with head and neck cancer who were to receive radiotherapy alone or radiotherapy plus chemotherapy. This is a final report of the findings.

2. STUDY OBJECTIVES

The objectives of this Phase 1 study were to evaluate oral MRX-1024 in patients with head and neck cancer who were to receive radiation alone or radiation plus chemotherapy. Endpoints of the study included describing the safety of MRX-1024 and the incidence and severity of oral mucositis resulting from concomitant radiation and chemotherapy.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This was a single-center, non-randomized, open-label, multiple dose, Phase 1 pilot study conducted at Nizam's Institute of Medical Sciences, Hyderabad, India. Patients with head and neck cancer who were about to receive standard therapy with radiation alone or radiation plus chemotherapy were screened versus the eligibility criteria. Eligible and

consenting patients received oral doses of MRX-1024 suspension two times daily, before and immediately after radiation fractions.

3.2. Protocol Amendments

The original protocol specified 3 dose levels would be tested (25 mg/kg, 50 mg/kg, and 100 mg/kg), using a single daily dose given prior to each radiation fraction. An updated protocol, in effect before the first patient was enrolled, specified that these same doses would be given twice daily, one hour before and again 15 minutes after each radiation fraction. A protocol amendment was approved by the sponsor (March 9, 2004) to treat all patients beyond Patient Number 1 with a dose of 100 mg/kg given twice a day. This change was made because Patient Number 1, treated at 25 mg/kg, developed Grade 3 oral mucositis and the Radiation Oncologists and the Investigator became concerned that the 25 mg/kg and 50 mg/kg doses would be subtherapeutic in preventing oral mucositis. In addition, this change was supported by the known safety of therapeutic doses of DL-methionine in the treatment of acetaminophen overdose.

3.3. Institutional Review Board/Ethics Committee (IRB/EC)

The original protocol and consent documents were approved by the participating center's IRB/EC. Written informed consent was required from each patient who participated in the study, or his/her authorized representative, prior to the patient's study enrollment. The informed consent form was to be signed, witnessed, and dated.

3.4. Patient Selection

3.4.1. Inclusion Criteria

To enter the study, patients must have met the following major inclusion criteria.

- Male or female, ages 18-65 years, inclusive;
- Histologically confirmed diagnosis of head and neck cancer;

- Planned therapy with radiation to at least 50% of the oral pharynx, or radiation plus chemotherapy;
- Females must be either surgically sterile, more than 12 months post-menopausal and not on hormone replacement therapy, or be prepared to practice a double barrier form of birth control from the screening visit through to 30 days after the last dose of study medication;
- Karnofsky Performance Score (KPS) $\geq$ 60;
- Willing and able to give written informed consent.

3.4.2. Exclusion Criteria

Patients were excluded from participation who met any of the following major exclusion criteria.

- T1 or T2 glottic tumors; tumor limited to vocal chords; tumor extending to supraglottis and/or impaired vocal cord mobility;
- Current evidence or history of clinically significant acute or unstable medical conditions, as specified in the protocol;
- Surgical or medical condition that may interfere with oral drug absorption;
- Previous exposure to methionine;
- Inadequate liver or renal function, defined as bilirubin or creatinine values >2 times the upper limit of normal; SGOT (AST), SPGT (ALT) or alkaline phosphatase >3 times the upper limit of normal;
- Inadequate hematology parameters, defined as WBC <3.5 x $10^3/\mu L$, platelet count <100 x $10^3/\mu L$, hemoglobin <9 g/dL, hematocrit <27%, or serum albumin <2.5 g/dL;
- Pregnant, lactating, breast feeding, or planning to conceive or father a child in the period surrounding the study;
- Prior exposure to radiotherapy.

3.4.3. Guidelines for Patient Withdrawal

All patients had the right to withdraw from the study at any time. Patients meeting the following criteria in the opinion of the investigator must be withdrawn from the study:

- Experiencing a serious or severe adverse event;
- Concurrent illness or requirement for prohibited medication.

Patients withdrawing for reasons related to study drug (usually adverse events) will be regarded as having completed the study and will not be replaced. Patients withdrawing for other reasons earlier than Study Visit 4 may be replaced, to a maximum of 6 patients, at the Investigator's discretion.

3.5. Study Treatment

3.5.1. Radiation

Radiation was delivered to each patient in the Cobalt machine room, Department of Radiation Oncology, at the participating center. Patients were to receive exposures of 1.8-2.0 Gy daily for 5 consecutive days each week until a total of 60 Gy had been delivered. Patients were treated using a Telecobalt Machine (Theratronics), manufactured by Atomic Energy of Canada Ltd, Canada. The source used was *COBALT 60.*

3.5.2. Chemotherapy

Patients designated by the Investigator to receive chemotherapy in addition to radiation received up to five weekly doses of cisplatin. Patients were pretreated with ondansetron (4 to 8 mg) with or without domperidone (4 mg). Cisplatin, 50 mg/m^2 mixed in 500 mL Normal Saline, was administered over 40 minutes. Following each cisplatin infusion, an additional 500 mL of Normal Saline containing 20 mEq of potassium chloride and 50 mEq of magnesium sulfate was infused over 40 minutes.

3.5.3. MRX-1024

3.5.3.1. Dose Levels, Number of Patients

The dose range of MRX-1024 of 25 to 100 mg/kg per dose was selected based on the safety of the recommended dose of DL-methionine used in treating acetaminophen overdosage [(2.5 to 10 g.) Therapeutic Drugs, Edited by Sir Colin Dollery, Churchill Livingstone Publication, 1991].

A total of 18 patients were required to complete the study as per protocol. Additional patients may be enrolled to serve as replacements for patients dropping out prior to Study Visit 4 for reasons other than adverse events. A total of 25 patients were enrolled. This final report summarizes data received on all 25 patients.

3.5.3.2. Method of Administration

MRX-1024 was provided by Molecular Therapeutics as a suspension formulation for oral use at a concentration of 200 mg/mL, developed by Natco Pharma Ltd, Banjara Hills, Hyderabad, Andhra Pradesh. The suspension was stored at controlled ambient room temperature in a securely locked enclosure.

On the first day of treatment the patient was weighed and his/her individual dose and corresponding volume of suspension was calculated. Study personnel shook the bottle of MRX-1024 to evenly suspend the contents and then measured the correct dose using a 50 mL beaker.

Example: A study patient who weighed 60 kg and who was to receive a dose of 100 mg/kg would receive a dose of 6000 mg of MRX-1024. This dose would be contained in a suspension volume of 30 mL.

Each measured dose was administered directly to the patient at the study center by study personnel. Patients were not allowed to self-medicate with MRX-1024. No period of fasting was required prior to or following doses of MRX-1024.

The batch number of MRX-1024 used throughout this study was RAD/SUSP/1024/200/005.

3.6. Efficacy and Safety Variables

3.6.1. Study Assessments

Potential study participants were screened versus the eligibility criteria. Eligible and consenting study patients completed a pretreatment evaluation that included a physical examination with a thorough oral examination, medical history, measurement of vital signs, electrocardiogram, KPS evaluation, blood and urine collection, and a serum pregnancy test when appropriate. X-rays were optional. Patients received treatment as described in Section 3.5. Follow-up visits were conducted weekly through the completion of radiation and chemotherapy treatment, as shown below:

- Screening Visit (day –21 to Study Day 1)
- Baseline Visit (before first dose on Study Day 1)
- Study Day 1 – treatment begins
- Visit 2 - after treatment was completed in Week 1
- Visit 3 - after treatment was completed in Week 2
- Visit 4 - after treatment was completed in Week 3
- Visit 5 - after treatment was completed in Week 4
- Visit 6 - after treatment was completed in Week 5
- Visit 7 - 7 days after last dose.

Adverse events were documented as reported during each visit. Efficacy parameters with respect to the development of oral mucositis were obtained at each visit using the scoring

systems described below. An evaluation of antitumor activity was conducted at the end of the treatment period. Post-treatment assessments included a physical examination, review of adverse events, measurement of vital signs, hematology and chemistry laboratory values, and a final assessment of efficacy variables.

Secondary outcome variables described in the protocol (viability of buccal cells, epithelial cell morphology and differentiation, neutrophil levels in mouth washings, salivary flow test) were carried out as and when possible as an academic exercise. These parameters were additional and optional since the validity of these tests are not established.

3.6.2. Efficacy Assessments for Oral Mucositis

The study was conducted using the following validated, standardized scoring systems. These scales were administered at the Baseline Visit and at every scheduled visit thereafter:

- National Cancer Institute Common Toxicity Criteria (NCI-CTC) for Grading of Stomatitis
- World Health Organization (WHO) Index Scale
- Radiation Therapy Oncology Group (RTOG) Oral Mucositis Grading System
- Objective Scoring System for Site Assessment.

National Cancer Institute Common Toxicity Criteria Grading Of Stomatitis

Grade	Grade Criteria
1	Painless ulcers, erythema, or mild soreness
2	Painful erythema, edema, or ulcers but ability to eat
3	Painful erythema, edema, or ulcers and inability to eat
4	Parenteral or enteral support

World Health Organization Index Scale

Grade	Description
0	No mucositis
1	Painless ulcer, erythema or mild soreness
2	Painful erythema, edema, ulcer, but can eat.
3	Painful erythema, edema, ulcer, but cannot eat.
4	Required parenteral or enteral support.

Radiation Therapy Oncology Group Oral Mucositis Grading System

Score	Gross Physician Rating	Functional Patient Rating
0	None	None
1	Erythmatous sores	Mild soreness, mild dysphasia, solid diet possible
2	Patchy mucositis (< ½ mucosa)	Moderate pain, moderate dysphasia, soft diet or liquid diet possible
3	Confluent fibrinous mucositis (>1/2 mucosa)	Severe pain, severe dysphasia, liquids only.
4	Hemorrhage and necrosis	Requires parenteral or enteral support

Objective Scoring System For Site Assessment

Site No.	Location	Ulceration/Pseudomembrane Score				Erythema Score		
1	Upper lip	0	1	2	3	0	1	2
2	Lower lip	0	1	2	3	0	1	2
3	Right cheek	0	1	2	3	0	1	2
4	Left cheek	0	1	2	3	0	1	2
5	Right ventral and lateral tongue	0	1	2	3	0	1	2
6	Left ventral and lateral tongue	0	1	2	3	0	1	2
7	Floor of mouth	0	1	2	3	0	1	2
8	Soft palate / fauces	0	1	2	3	0	1	2
9	Hard palate	0	1	2	3	0	1	2

Ulceration

0 = no lesion 2 = 1-3 cm^2

1 = <1 cm^2 3 = >3 cm^2

Erythema

0 = none

1 = not severe 2 = severe

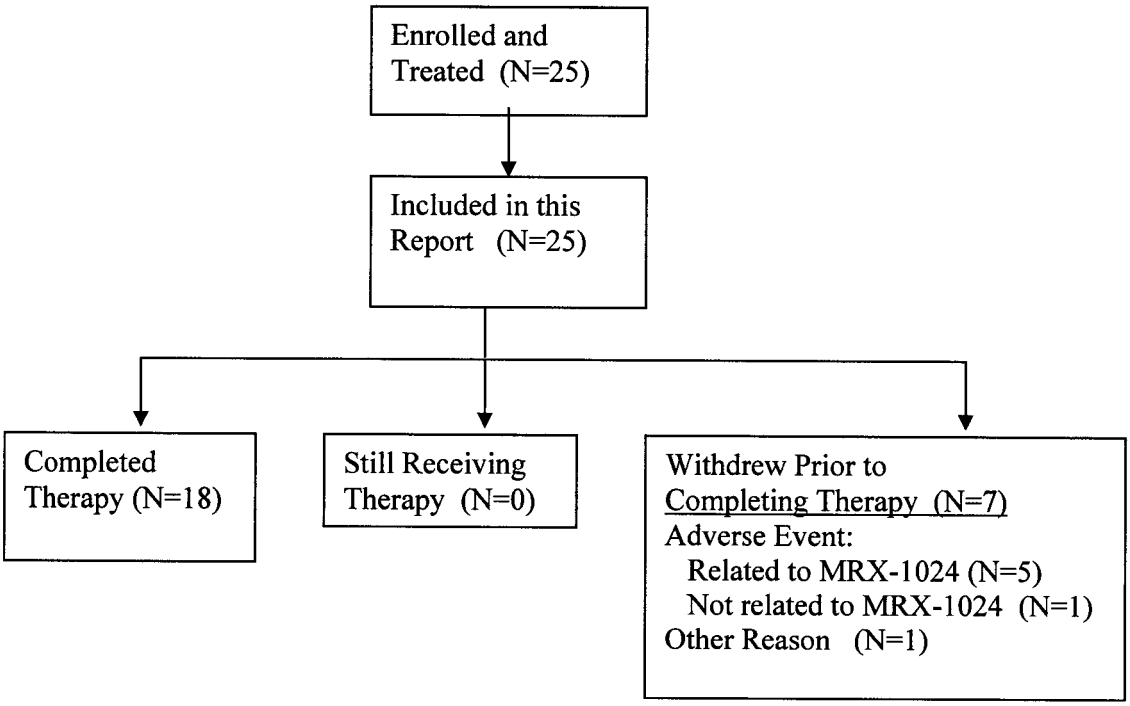
4. STUDY PATIENTS

The Ethics Committee approved the protocol on November 20, 2003. The first patient was enrolled on March 3, 2004. The last patient (Patient Number 25) was enrolled on July 2, 2004. All patients have completed their participation on this protocol.

4.1. Disposition of Patients

Twenty-five patients were enrolled on this study. Figure 1 summarizes the disposition of all 25 patients.

FIGURE 1. Patient Disposition



4.2. Patient Demographics

Table 1 displays the demographic data from all 25 patients. All patients had head and neck cancer with the exception of Patient No. 23, diagnosed with Non-Hodgkin's Lymphoma confined to cervical lymphadenopathy, for whom localized radiation was considered appropriate therapy. There were 15 males and 10 females. Median age was 47 years. Median weight was 55 kg. The baseline Karnofsky Performance Status was generally good, with 19 patients (76%) having a baseline KPS of at least 80.

Table 1. Listing of Baseline Patient Demographic Data

Patient Number/initials	Head & Neck Cancer Site	Gender	Age (years)	Weight (kg)	KPS
1 / VRM	Tongue	Female	61	57	80
2 / MKR	Post Cricoid (oral pharynx)	Male	50	54	60
3 / MSR	Tongue	Female	45	65	80
4 / KSA	Hypopharynx	Female	38	42	60
5 / MSRR	Palate	Male	58	42	80
6 / MK	Tonsil	Female	65	60	70
7 / GSN	Pharynx	Male	52	55	60
8 / ZBE	Cheek	Female	62	65	70
9 / JR	Post Cricoid (oral pharynx)	Male	55	41	60
10 / MDS	Hypopharynx	Male	40	45	90
11 / BRK	Nasopharynx	Male	53	55	80
12 / VLX	Post Cricoid (oral pharynx)	Female	45	70	90
13 / BLM	Maxilla	Female	40	55	90
14 / GST	Salivary gland	Female	37	48	90
15 / CHM	Palate	Female	40	45	90
16 / PLA	Salivary gland	Female	45	45	90
17 / PRH	Floor of mouth	Male	65	50	90
18 / JKD	Cheek	Male	47	64	90
19 / KSS	Tongue	Male	39	65	90
20 / CGR	Cheek	Male	45	65	90
21 / BSL	Hypopharyngeal	Male	40	52	90
22 / MDI	Cheek	Male	56	85	80
23 / TNR	Non-Hodgkin's Lymphoma	Male	38	68	90
24 / YVR	Post Cricoid (oral pharynx)	Male	49	50	90
25 / MKRR	Tonsil	Male	60	45	80

5. RESULTS

5.1. Listings of Results

5.1.1. Treatment Administered

Table 2 lists the treatment received by all 25 patients. Six patients received radiation alone; nineteen patients received radiation plus chemotherapy.

Table 2. Listing of Treatment Administered

Pt. No.	Radiation Dose/Day (Gy)	No. Fractions Completed/ Total Radiation Dose Delivered	MRX-1024 (mg/kg/ dose) Given Twice Daily	No. Days MRX-1024 Given	No. Chemotherapy Cycles Given	Status
1	2.0	12 / 24 Gy	25	12	3	Developed mucositis; as a result refused to continue treatment
2	2.0	21 / 42 Gy	100	21	3	Completed[a]
3	2.0	30 / 60 Gy	100	30	5	Completed
4	2.0	30 / 60 Gy	100	30	1	Completed
5	2.0	30 / 60 Gy	100	30	5	Completed
6	2.0	3 / 6 Gy	100	3	0	Withdrew due to AE (nausea)
7	2.0	30 / 60 Gy	100	30	4	Completed
8	2.0	14 / 28 Gy	100	14	2	Withdrew due to AE (nausea)
9	2.0	30 / 60 Gy	100	30	5	Completed
10	2.0	10 / 20 Gy	100	10	1	Lost to follow-up. Pt did not return to clinic for unknown reason.
11	1.8	20 / 36 Gy	100	20	0	Completed[a]
12	1.8	23 / 41.4 Gy	100	23	4	Completed[a]
13	1.8	30 / 54 Gy	100	30	5	Completed
14	1.8	28 / 50.4 Gy	100	28	0	Completed[a]
15	2.0	30 / 60 Gy	100	30	3	Completed
16	2.0	5 / 10 Gy	100	5	0	Withdrew due to AE (nausea)

17	2.0	21 / 42 Gy	100	21	3	Completed[a]
18	2.0	30 / 60 Gy	100	30	0	Completed
19	2.0	20 / 40 Gy	100	20	3	Completed[a]
20	1.8	4 / 7.2 Gy	100	4	1	Withdrew due to AE (nausea)
21	2.0	4 / 8.0 Gy	100	4	1	Withdrew due to AE (nausea)
22	2.0	30 / 60 Gy	100	28	4	Completed
23	2.0	22 / 44 Gy	100	22	0	Completed[a]
24	2.0	27 / 54 Gy	100	27	3	Completed[a]
25	2.0	30 / 60 Gy	100	30	3	Completed

AE = adverse event

[a] Discontinued radiation prior to 30 fractions, but considered to have completed the study.

Patient Number 1 is the only patient to have received MRX-1024 at the 25 mg/kg dose (given twice daily). All subsequent patients were treated according to the protocol amendment at 100 mg/kg per dose, administered before and again after each day's radiation fraction.

Eighteen patients (72%) are considered to have completed their intended course of radiation, defined as having received at least 20 fractions. Ten patients (40%) received 30 fractions to a total dose of 54-60 Gy. Nine of these patients received concomitant chemotherapy.

5.1.2. Primary Efficacy Evaluations for Oral Mucositis

The following tables report the occurrence, or lack thereof, of oral mucositis as assessed by the Investigator using the WHO (Table 3), NCI-CTC (Table 4), RTOG [Tables 5a (Physician rated) and 5b (Patient rated)], and Objective Scoring System for Site Assessment scales [Tables 6a through 6e (Ulceration) and 7a through 7e (Erythema)]. Data are presented for all 25 patients.

Table 3. Results Using WHO Scoring System for Oral Mucositis

(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Follow up Visit
1	RT+CT	No	0	2	3	---	---	---	---
2	RT+CT	Yes	0	0	0	0	---	---	---
3	RT+CT	Yes	0	0	1	0	0	0	0
4	RT+CT	Yes	0	0	0	1	0	0	0
5	RT+CT	Yes	0	0	0	1	0	0	0
6	RT	No	0	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	2	---
8	RT+CT	No	0	0	0	---	---	---	---
9	RT+CT	Yes	0	0	0	0	1	1	---
10	RT+CT	No	0	0	---	---	---	---	---
11	RT	Yes	0	0	0	0	---	---	---
12	RT+CT	Yes	0	0	1	2	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	---	---
15	RT+CT	Yes	0	0	1	1	1	1	---
16	RT	No	0	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	---	---	---
18	RT	Yes	0	0	0	1	1	1	---
19	RT+CT	Yes	0	0	0	2	---	---	---
20	RT+CT	No	0	---	---	---	---	---	---
21	RT+CT	No	0	---	---	---	---	---	---
22	RT+CT	Yes	0	0	1	2	3	3	---
23	RT	Yes	0	0	0	0	---	---	---
24	RT+CT	Yes	0	0	0	1	1	---	---
25	RT+CT	Yes	0	0	0	0	1	1	---

RT = Radiation therapy

CT = Chemotherapy

--- = Patient no longer being followed on study.

[a] Received at least 20 fractions

Table 4. Results Using NCI-CTC Scoring System for Oral Mucositis
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Follow up Visit
1	RT+CT	No	0	2	3	---	---	---	---
2	RT+CT	Yes	0	0	0	0	---	---	---
3	RT+CT	Yes	0	0	1	0	0	0	0
4	RT+CT	Yes	0	0	0	1	0	0	0
5	RT+CT	Yes	0	0	0	1	0	0	0
6	RT	No	0	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	2	0
8	RT+CT	No	0	0	0	---	---	---	---
9	RT+CT	Yes	0	0	0	0	1	1	---
10	RT+CT	No	0	0	---	---	---	---	---
11	RT	Yes	0	0	0	0	---	---	---
12	RT+CT	Yes	0	0	1	2	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	---	---
15	RT+CT	Yes	0	0	1	1	1	1	---
16	RT	No	0	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	---	---	---
18	RT	Yes	0	0	0	1	1	1	---
19	RT+CT	Yes	0	0	0	2	---	---	---
20	RT+CT	No	0	---	---	---	---	---	---
21	RT+CT	No	0	---	---	---	---	---	---
22	RT+CT	Yes	0	0	1	2	3	3	---
23	RT	Yes	0	0	0	0	---	---	---
24	RT+CT	Yes	0	0	0	1	1	---	---
25	RT+CT	Yes	0	0	0	0	1	1	---

RT = Radiation therapy
CT = Chemotherapy
--- = Patient no longer being followed on study.
[a] Received at least 20 fractions

Table 5a. Results Using RTOG Scoring System, Gross Physician Rating, for Oral Mucositis (Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Follow up Visit
1	RT+CT	No	0	2	3	---	---	---	---
2	RT+CT	Yes	0	0	0	0	---	---	---
3	RT+CT	Yes	0	0	1	0	0	0	0
4	RT+CT	Yes	0	0	0	1	0	0	0
5	RT+CT	Yes	0	0	0	1	0	0	0
6	RT	No	0	---	---	---	---	---	
7	RT+CT	Yes	0	0	0	0	0	2	0
8	RT+CT	No	0	0	0	---	---	---	---
9	RT+CT	Yes	0	0	0	0	1	1	---
10	RT+CT	No	0	0	---	---	---	---	---
11	RT	Yes	0	0	0	0	---	---	---
12	RT+CT	Yes	0	0	1	2	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	---	---
15	RT+CT	Yes	0	0	1	1	1	1	---
16	RT	No	0	---	---	---	---	---	
17	RT+CT	Yes	0	0	0	0	---	---	---
18	RT	Yes	0	0	0	1	1	1	---
19	RT+CT	Yes	0	0	0	2	---	---	---
20	RT+CT	No	0	---	---	---	---	---	---
21	RT+CT	No	0	---	---	---	---	---	---
22	RT+CT	Yes	0	0	1	2	3	3	---
23	RT	Yes	0	0	0	0	---	---	---
24	RT+CT	Yes	0	0	0	1	1	---	---
25	RT+CT	Yes	0	0	0	0	1	1	---

RT = Radiation therapy
CT = Chemotherapy
--- = Patient no longer being followed on study.
[a] Received at least 20 fractions

Table 5b. Results Using RTOG Scoring System, Functional Patient Rating, for Oral Mucositis (Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Follow up Visit
1	RT+CT	No	0	2	3	---	---	---	---
2	RT+CT	Yes	0	0	0	0	---	---	---
3	RT+CT	Yes	0	0	1	0	0	0	0
4	RT+CT	Yes	0	0	0	1	0	0	0
5	RT+CT	Yes	0	0	0	1	0	0	0
6	RT	No	0	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	2	---
8	RT+CT	No	0	0	0	---	---	---	---
9	RT+CT	Yes	0	0	0	0	1	1	---
10	RT+CT	No	0	0	---	---	---	---	---
11	RT	Yes	0	0	0	0	---	---	---
12	RT+CT	Yes	0	0	1	2	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	---	---
15	RT+CT	Yes	0	0	1	1	1	1	---
16	RT	No	0	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	--	---	---
18	RT	Yes	0	0	0	1	1	1	---
19	RT+CT	Yes	0	0	0	2	---	---	---
20	RT+CT	No	0	---	---	---	---	---	---
21	RT+CT	No	0	---	---	---	---	---	---
22	RT+CT	Yes	0	0	1	2	3	3	---
23	RT	Yes	0	0	0	0	---	---	---
24	RT+CT	Yes	0	0	0	1	1	---	---
25	RT+CT	Yes	0	0	0	0	1	1	---

See Table 5a for abbreviations and footnotes.

Table 6a. Results Using Objective Scoring System (Ulceration) – Baseline
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	0	0	0	0	0	0	0	0	0
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	0	0	0	0	0	0	0	0	0
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	0	0	0	0	0	0	0	0	0
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	0	0	0	0	0	0	0	0	0
11	RT	Yes	0	0	0	0	0	0	0	0	0
12	RT+CT	Yes	0	0	0	0	0	0	0	0	0
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	0	0	0	0	0	0	0
16	RT	No	0	0	0	0	0	0	0	0	0
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	0	0	0	0	0	0
19	RT+CT	Yes	0	0	0	0	0	0	0	0	0
20	RT+CT	No	0	0	0	0	0	0	0	0	0
21	RT+CT	No	0	0	0	0	0	0	0	0	0
22	RT+CT	Yes	0	0	0	0	0	0	0	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

RT = Radiation therapy CT = Chemotherapy
[a] Received at least 20 fractions
UL = upper lip LL = Lower lip RC = Right cheek
LC = Left cheek RVLT = Right ventral and lateral tongue
LVLT = Left ventral and lateral tongue FM = Floor of mouth
SP = Soft palate HP = Hard palate

Table 6b. Results Using Objective Scoring System (Ulceration) – Visit 2
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	0	0	2	2	0	0	2	0	0
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	0	0	0	0	0	0	0	0	0
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	0	0	0	0	0	0	0	0	0
11	RT	Yes	0	0	0	0	0	0	0	0	0
12	RT+CT	Yes	0	0	0	0	0	0	0	0	0
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	0	0	0	0	0	0	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	1	0	0	0	0	0
19	RT+CT	Yes	0	0	0	0	0	0	0	0	0
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	0	0	0	0	0	0	0	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 6a for abbreviations and footnotes.

Table 6c. Results Using Objective Scoring System (Ulceration) – Visit 3
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	0	2	0	0	3	2	2	2	0
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	0	0	0	0	0	0	0	0	0
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	0	0	0	0	0	0	0	0	0
12	RT+CT	Yes	0	0	0	0	1	1	0	0	0
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	2	1	1	1	0	0	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	0	0	0	0	0	0
19	RT+CT	Yes	0	0	0	0	0	0	0	0	0
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	0	0	0	0	0	0	0	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 6a for abbreviations and footnotes.

Table 6d. Results Using Objective Scoring System (Ulceration) – Visit 4
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	---	---	---	---	---	---	---	---	---
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	1	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	---	---	---	---	---	---	---	---	---
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	---	---	---	---	---	---	---	---	---
12	RT+CT	Yes	0	0	2	2	2	2	1	1	1
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	2	1	1	1	1	1	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	1	0	0	0	0	0
19	RT+CT	Yes	2	2	1	0	0	0	0	0	0
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	0	0	1	1	1	1	0	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 6a for abbreviations and footnotes.

Table 6e. Results Using Objective Scoring System (Ulceration) – Visit 5
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	---	---	---	---	---	---	---	---	---
2	RT+CT	Yes	---	---	---	---	---	---	---	---	---
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	---	---	---	---	---	---	---	---	---
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	---	---	---	---	---	---	---	---	---
12	RT+CT	Yes	---	---	---	---	---	---	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	1	1	1	1	1	1	1	1	1
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	---	---	---	---	---	---	---	---	---
18	RT	Yes	0	0	0	1	0	0	0	0	0
19	RT+CT	Yes	---	---	---	---	---	---	---	---	---
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	0	2	2	2	2	2	0	0	0
23	RT	Yes	---	---	---	---	---	---	---	---	---
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 6a for abbreviations and footnotes.

Table 6f. Results Using Objective Scoring System (Ulceration) – Visit 6

(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	---	---	---	---	---	---	---	---	---
2	RT+CT	Yes	---	---	---	---	---	---	---	---	---
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	2	1	1	1	2	1	1
8	RT+CT	No	---	---	---	---	---	---	---	---	---
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	---	---	---	---	---	---	---	---	---
12	RT+CT	Yes	---	---	---	---	---	---	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	---	---	---	---	---	---	---	---	---
15	RT+CT	Yes	1	1	1	1	0	0	0	0	1
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	---	---	---	---	---	---	---	---	---
18	RT	Yes	0	0	0	1	0	0	0	0	0
19	RT+CT	Yes	---	---	---	---	---	---	---	---	---
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	0	0	2	2	2	2	0	0	0
23	RT	Yes	---	---	---	---	---	---	---	---	---
24	RT+CT	Yes	---	---	---	---	---	---	---	---	---
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 6a for abbreviations and footnotes.

Table 7a. Results Using Objective Scoring System (Erythema) – Baseline
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	0	0	0	0	0	0	0	0	0
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	0	0	0	0	0	0	0	0	0
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	0	0	0	0	0	0	0	0	0
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	0	0	0	0	0	0	0	0	0
11	RT	Yes	0	0	0	0	0	0	0	0	0
12	RT+CT	Yes	0	0	0	0	0	0	0	0	0
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	0	0	0	0	0	0	0
16	RT	No	0	0	0	0	0	0	0	0	0
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	0	0	0	0	0	0
19	RT+CT	Yes	0	0	0	0	0	0	0	0	0
20	RT+CT	No	0	0	0	0	0	0	0	0	0
21	RT+CT	No	0	0	0	0	0	0	0	0	0
22	RT+CT	Yes	0	0	0	0	0	0	0	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

RT = Radiation therapy
CT = Chemotherapy
[a] Received at least 20 fractions
UL = upper lip
LL = Lower lip
RC = Right cheek
LC = Left cheek
RVLT = Right ventral and lateral tongue
LVLT = Left ventral and lateral tongue
FM = Floor of mouth
SP = Soft palate
HP = Hard palate

Table 7b. Results Using Objective Scoring System (Erythema) – Visit 2

(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	0	2	2	2	0	0	2	0	0
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	0	0	0	0	0	0	0	0	0
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	0	0	0	0	0	0	0	0	0
11	RT	Yes	0	0	0	0	0	0	0	0	0
12	RT+CT	Yes	0	0	0	0	0	0	0	0	0
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	0	0	0	0	0	0	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	0	0	0	0	0	0
19	RT+CT	Yes	0	0	0	0	0	0	0	0	0
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	0	0	0	0	0	0	0	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 7a for abbreviations and footnotes.

Table 7c. Results Using Objective Scoring System (Erythema) – Visit 3
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	0	2	2	2	2	2	2	2	2
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	1	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	0	0	0	0	0	0	0	0	0
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	0	0	0	0	0	0	0	0	0
12	RT+CT	Yes	0	0	0	0	0	1	0	0	0
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	1	1	1	1	0	0	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	0	0	0	0	0	0
19	RT+CT	Yes	0	0	0	0	0	0	0	0	0
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	0	0	1	1	1	1	0	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	0	0	0	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 7a for abbreviations and footnotes.

Table 7d. Results Using Objective Scoring System (Erythema) – Visit 4
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	---	---	---	---	---	---	---	---	---
2	RT+CT	Yes	0	0	0	0	0	0	0	0	0
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	1	1	0	1	0	0	0	0	0
5	RT+CT	Yes	0	0	1	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	---	---	---	---	---	---	---	---	---
9	RT+CT	Yes	0	0	0	0	0	0	0	0	0
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	0	0	0	0	0	0	0	0	0
12	RT+CT	Yes	0	0	2	2	2	2	0	0	0
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	0	0	1	1	1	1	0	0	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	0	0	0	0	0	0	0	0	0
18	RT	Yes	0	0	0	1	0	0	0	0	0
19	RT+CT	Yes	2	2	1	1	1	1	1	1	1
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	1	1	2	2	2	1	1	0	0
23	RT	Yes	0	0	0	0	0	0	0	0	0
24	RT+CT	Yes	1	0	1	0	0	0	0	0	0
25	RT+CT	Yes	0	0	0	0	0	0	0	0	0

See Table 7a for abbreviations and footnotes.

Table 7e. Results Using Objective Scoring System (Erythema) – Visit 5
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]?	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	---	---	---	---	---	---	---	---	---
2	RT+CT	Yes	---	---	---	---	---	---	---	---	---
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	0	0	0	0	0	0	0
8	RT+CT	No	---	---	---	---	---	---	---	---	---
9	RT+CT	Yes	0	0	0	0	0	0	0	0	1
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	---	---	---	---	---	---	---	---	---
12	RT+CT	Yes	---	---	---	---	---	---	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	0	0	0	0	0	0	0	0	0
15	RT+CT	Yes	1	0	0	1	1	1	0	0	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	---	---	---	---	---	---	---	---	---
18	RT	Yes	0	0	0	1	0	0	0	0	0
19	RT+CT	Yes	---	---	---	---	---	---	---	---	---
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	2	2	2	2	1	2	1	1	2
23	RT	No	---	---	---	---	---	---	---	---	---
24	RT+CT	Yes	1	0	1	0	0	0	0	0	0
25	RT+CT	Yes	0	0	1	1	1	1	0	0	0

See Table 7a for abbreviations and footnotes.

Table 7f. Results Using Objective Scoring System (Erythema) – Visit 6
(Values shown are toxicity grades)

Patient No.	Treatment (RT or RT+CT)	Completed Therapy[a]	UL	LL	RC	LC	RVLT	LVLT	FM	SP	HP
1	RT+CT	No	---	---	---	---	---	---	---	---	---
2	RT+CT	Yes	---	---	---	---	---	---	---	---	---
3	RT+CT	Yes	0	0	0	0	0	0	0	0	0
4	RT+CT	Yes	0	0	0	0	0	0	0	0	0
5	RT+CT	Yes	0	0	0	0	0	0	0	0	0
6	RT	No	---	---	---	---	---	---	---	---	---
7	RT+CT	Yes	0	0	2	0	0	0	2	0	0
8	RT+CT	No	---	---	---	---	---	---	---	---	---
9	RT+CT	Yes	0	0	0	1	0	0	0	0	0
10	RT+CT	No	---	---	---	---	---	---	---	---	---
11	RT	Yes	---	---	---	---	---	---	---	---	---
12	RT+CT	Yes	---	---	---	---	---	---	---	---	---
13	RT+CT	Yes	0	0	0	0	0	0	0	0	0
14	RT	Yes	---	---	---	---	---	---	---	---	---
15	RT+CT	Yes	0	1	1	1	0	0	0	1	0
16	RT	No	---	---	---	---	---	---	---	---	---
17	RT+CT	Yes	---	---	---	---	---	---	---	---	---
18	RT	Yes	0	0	0	1	0	0	0	0	0
19	RT+CT	Yes	---	---	---	---	---	---	---	---	---
20	RT+CT	No	---	---	---	---	---	---	---	---	---
21	RT+CT	No	---	---	---	---	---	---	---	---	---
22	RT+CT	Yes	2	2	2	2	1	2	1	1	2
23	RT	No	---	---	---	---	---	---	---	---	---
24	RT+CT	Yes	1	0	1	0	0	0	0	0	0
25	RT+CT	Yes	0	0	1	1	1	1	0	0	0

See Table 7a for abbreviations and footnotes.

5.1.3. Adverse Events

Table 8 lists the adverse events, by grade, attributability, and outcome, as reported by all 25 patients. Clinical laboratory deviations are included in the table, without grade, attributability, or outcome assessments.

Table 8. Listing of Adverse Events

Patient No.	Treatment (RT or RT+CT)	MRX-1024 (mg/kg/ dose)	AE	Visit of AE	Description of AE	Grade	Relation to MRX-1024	Action	Outcome Code	Status
1	RT+CT	25	Yes	Visit 2 Visit 2	Vomiting Feels Very Weak	2 2	Not Related Not Related	Treated Treated	3 3	Developed mucositis; as a result refused to continue treatment
2	RT+CT	100	Yes	Visit 2	Dysphasia	2	Not Related	Treated	3	Completed[a]
3	RT+CT	100	Yes	Between Visit 1 and Visit 2	Vomiting <u>Change in Lab Parameter:</u> ↓RBC: 4.06 x10^6/μL ↑Neutrophils: 77% ↓Lymphocytes: 15%	1	Not Related	Treated	1	Completed
4	RT+CT	100	Yes	After screening and before drug administration Visit 4	Fever Vomiting <u>Change in Lab Parameter</u>	2 2	Not Related Not Related	Treated Treated	2 1	Completed

					↓Lymphocytes: 19%					
5	RT+CT	100	Yes	Visit 2 Visit 3 Visit 3	Vomiting Weakness Body Pain <u>Change in Lab Parameter</u> ↓RBC: 3.89 x10^6/μL ↓Lymphocytes: 12% ↑Monocytes: 11%	3 2 2	Not Related Not Related Not Related	Treated Treated None	2 3 3	Completed
6	RT	100	Yes	Day 2	Vomiting	2	Probably	Withdrawn	3	Withdrawn (AE)
7	RT+CT	100	Yes	Visit 3 Visit 4 Visit 4	Vomiting Vomiting Oropharyngeal Candidiasis <u>Change in Lab Parameter</u> ↑Neutrophil: 80% ↓Lymphocytes: 6% ↑Glucose Fasting: 111 mg/dL ↑SGOT: 74 U/L ↑SGPT: 68 U/L	1 3 3	Not Related Not Related Not Related	None Treated Treated	1 3 2	Completed

8	RT+CT	100	Yes	Visit 2 Visit 3	Vomiting Vomiting	1 2	Probably Probably	Withdrawn Withdrawn	1 3	Withdrawn (AE)
9	RT+CT	100	Yes	Visit 2	Vomiting <u>Change in Lab Parameter:</u> ↑RBC Count: 3.77 x10^6/μL ↓Lymphocytes: 14% ↓Platelet count: 517 x10^3/μL ↑Glucose Fasting: 159 mg/dL	1	Not Related	Treated	3	Completed
10	RT+CT	100	Yes	Visit 2	Weakness	2	Not Related	Treated	3	Lost to follow-up
11	RT	100	Yes	Visit 2	Nausea	2	Possibly	Treated	3	Completed[a]
12	RT+CT	100	Yes	Visit 2 Visit 3	Vomiting Fungal Infection	2 3	Not Related Not Related	Treated Treated	3 2	Completed[a]
13	RT+CT	100	Yes	Visit 4	Weakness <u>Change in Lab Parameter:</u> ↓RBC count: 3.74 x10^6/μL ↓MCHC: 32.7 g/dL	2	Not Related	Dose adjusted	3	Completed

					↑Neutrophil: 87% ↓Lymphocytes: 9%					
14	RT	100	Yes	Visit 3	Vomiting	1	Not Related	Treated	2	Completed[a]
15	RT	100	Yes	Visit 3	Fever	1	Not Related	Treated	2	Completed
				Visit 3	Body pains	1	Not Related	Treated	2	
				Visit 3	Weakness	1	Not Related	Treated	2	
					<u>Change in Lab Parameter:</u> ↓WBC Count: 2900/μL ↓RBC count: 6.68 x10^6/μL ↓Hb: 8.8 g/dL ↓Platelets: 26 x10^3/μL					
16	RT	100	Yes	Day 1	Vomiting	3	Probably	Withdrawn	3	Withdrawn (AE)
17	RT+CT	100	No	No	None	--	--	--	--	Completed[a]
18	RT	100	Yes	Visit 4	Fungal Infection	1	Not Related	Treated	2	Completed
19	RT+CT	100	Yes	Visit 2	Fungal Infection	2	Not Related	Treated	2	Completed[a]
				Visit 3	Weakness	2	Not Related	Treated	3	
					Vomiting	2	Not Related	Treated	3	
20	RT+CT	100	Yes	Visit 2	Vomiting	2	Possibly	Treated	3	Withdrawn

										(AE)
21	RT+CT	100	Yes	Visit 2	Vomiting	2	Probably	Treated	3	Withdrawn (AE)

22	RT+CT	100	Yes	Visit 2	Vomiting <u>Change in Lab Parameter:</u> ↑SGOT(AST): 52 U/L (Normal Range: 15-37 U/L)	2	Possibly	Treated	3	Completed
23	RT	100	Yes	Visit 2	Nausea and Vomiting.	2	Not Related	Treated	3	Completed[a]
24	RT+CT	100	Yes	Visit 2	Nausea	2	Possibly	Treated	3	Completed[a]
25	RT+CT	100	Yes	Visit 2	Vomiting	2	Possibly	Treated	3	Completed

AE = adverse event

[a] Discontinued radiation prior to 30 fractions, but considered to have completed the study.

Outcome Codes:

1 = resolved without intervention
2 = resolved with intervention
3 = continuing
4 = patient died

5.1.4. Tumor Responses

Table 9 lists the tumor responses for the 10 patients who received 30 radiation fractions, as evaluated by the investigators at the completion of therapy.

Table 9. Tumor Responses

Patient Number	Treatment (RT or RT+CT)	Clinical Examination at the Completion of Treatment
3	RT+CT	Good response. There was small node at the completion of RT, but the biopsy report came back negative, suggestive of a good response
4	RT+CT	Good response: lesion regressed well
5	RT+CT	Good response: lesion regressed well
7	RT+CT	Good response: lesion regressed well
9	RT+CT	Good response: lesion regressed well
13	RT+CT	Not clearly documented
15	RT+CT	Good response: lesion regressed well
18	RT	Good response: lesion regressed well
22	RT+CT	Good response: lesion regressed well
25	RT+CT	Good response: lesion regressed well

RT = Radiation therapy
CT = Chemotherapy

5.2. Summaries of Results

5.2.1. Extent of Exposure to MRX-1024

Table 10 summarizes the extent of exposure to MRX-1024.

Table 10. Summary of Extent of Exposure to MRX-1024

Dose Level (mg/kg)	No. Patients	Total Number of Days MRX-1024 Was Administered					
		1-5	6-10	11-15	16-20	21-25	26-30
25	1	0	0	1	0	0	0
100	24	4	1	1	2	4	12

Sixteen of 24 patients (67%) treated at 100 mg/kg twice daily of MRX-1024 were able to receive at least 21 days of dosing in combination with radiation or radiation plus cisplatin chemotherapy.

5.2.2. Primary Efficacy Evaluations for Oral Mucositis

The summary of the mucositis-protecting property of MRX-1024 is based on data from 21 patients who had at least one oral cavity evaluation following the start of treatment: 18 patients considered to have completed therapy (received at least 20 fractions); 2 patients withdrawn prior to receiving 20 fractions due to an adverse event; and one patient lost to follow-up after receiving 10 days of treatment. Data from 2 patients receiving radiation alone (Patient Numbers 6 and 16) and 2 patients receiving radiation plus chemotherapy (Patient Numbers 20 and 21) are not included because they were withdrawn prior to the initial evaluation for oral mucositis at Visit 2. Table 11 combines results reported using either the WHO or the NCI-CTC grading scales because the results in all cases were identical across both systems.

Table 11. Summary of Effectiveness of MRX-1024 in Preventing Oral Mucositis: Worst Toxicity Grade Reported at Any Visit, Using the WHO or NCI-CTC Scales

Treatment	Number of Patients	Toxicity Grade				
		0	1	2	3	4
RT alone	4	3	1	0	0	0
RT + CT	17	5	7	3	2[a]	0
Total	21	8	8	3	2[a]	0

RT = Radiation therapy
CT = Chemotherapy
[a] Includes one patient who received MRX-1024 at a dose of 25 mg/kg. All other patients received 100 mg/kg.

Table 12. Summary of Effectiveness of MRX-1024 in Preventing Oral Mucositis: Worst Toxicity Grade Reported at Any Visit, Using the RTOG Gross Physician Rating Scale

Treatment	Number of Patients	Toxicity Grade				
		0	1	2	3	4
RT alone	4	3	1	0	0	0
RT + CT	17	5	7	3	2[a]	0
Total	21	8	8	3	2[a]	0

RT = Radiation therapy
CT = Chemotherapy
[a] Includes one patient who received MRX-1024 at a dose of 25 mg/kg. All other patients received 100 mg/kg.

Table 13. Summary of Effectiveness of MRX-1024 in Preventing Oral Mucositis: Worst Toxicity Grade Reported at Any Visit, Using the RTOG Functional Patient Rating Scale

Treatment	Number of Patients	Toxicity Grade				
		0	1	2	3	4
RT alone	4	3	1	0	0	0
RT + CT	17	5	7	3	2[a]	0
Total	21	8	8	3	2[a]	0

RT = Radiation therapy
CT = Chemotherapy
[a] Includes on patient who received MRX-1024 at a dose of 25 mg/kg. All other patients received 100 mg/kg.

Table 14. Summary of Effectiveness of MRX-1024 in Preventing Oral Mucositis: Worst Toxicity Grade Reported at Any Visit, at Any Site Within the Oral Cavity, Using the Ulceration Module of the Objective Scoring System

Treatment	Number of Patients	Toxicity Grade				
		0	1	2	3	4
RT alone	4	3	1	0	0	0
RT + CT	17	10	1	5	1[a]	0
Total	21	13	2	5	1[a]	0

RT = Radiation therapy
CT = Chemotherapy
[a] This patient received MRX-1024 at a dose of 25 mg/kg. All other patients received 100 mg/kg.

Table 15. Summary of Effectiveness of MRX-1024 in Preventing Oral Mucositis: Worst Toxicity Grade Reported at Any Visit, at Any Site Within the Oral Cavity, Using the Erythema Module of the Objective Scoring System

Treatment	Number of Patients	Toxicity Grade				
		0	1	2	3	4
RT alone	4	3	1	0	0	0
RT + CT	17	5	7	5[a]	0	0
Total	21	8	8	5[a]	0	0

RT = Radiation therapy
CT = Chemotherapy
[a] Includes one patient who received MRX-1024 at a dose of 25 mg/kg. All other patients received 100 mg/kg.

5.2.3. Adverse Events

All patients received MRX-1024 in combination with standard therapy consisting of radiation or radiation plus cisplatin chemotherapy. These standard therapies are associated with a wide range of adverse events. Without the benefit of a single-agent MRX-1024 study in healthy volunteers or a randomized controlled trial of the combination versus standard therapy, it is difficult to definitively describe the adverse event profile of MRX-1024. However, the adverse events reported in this study appear to be similar to adverse events expected to be reported in a population of head and neck cancer patients receiving standard radiation or radiation plus cisplatin chemotherapy, with the exception of a lower incidence and severity of oral mucositis.

Because documenting oral mucositis was a major objective of this study, these events were recorded as efficacy parameters and were not also recorded as adverse events. The most commonly reported adverse event was vomiting, reported in 17 of 25 (68%) patients despite the pre-treatment administration of antiemetics in those patients receiving cisplatin. These 17 patients' adverse event of vomiting was graded as Grade 1 in 3 patients, Grade 2 in 11 patients, and Grade 3 in 3 patients. Five patients were withdrawn from the study due to the adverse event of vomiting: Patient 6 on Day 2, Patient 8 at Visit 3, Patient 16 on Day 1, Patient 20 at Visit 2, and Patient 21 at Visit 2. Two additional patients reported Grade 2 nausea but no vomiting.

Additional adverse events included weakness (6 patients), fungal infection (4 patients), fever (2 patients), body pains (2 patients), and dysphagia (1 patient). These adverse events were all graded as Grade 1 or 2, with the exception of two Grade 3 adverse events: fungal infection and oral candidiasis, one patient each.

5.2.4. Serious, Nonfatal Adverse Events

No patients experienced a serious adverse event while on study or within 30 days of receiving their last treatment.

5.2.5. Deaths

No patients died while on study or within 30 days of receiving their last treatment.

5.2.6. Clinical Laboratory Evaluations

All patients received radiation to involved head and neck regions. Nineteen patients received concomitant cisplatin chemotherapy, an agent known to affect renal functions tests, hematology parameters, electrolyte values, and other laboratory parameters. Clinical laboratory testing was done only at baseline and again at the completion of therapy, not on an ongoing basis during the treatment period. Therefore, no database exists to definitively assess changes to clinical laboratory parameters caused by MRX-1024.

Table 8 (Adverse Events) includes those clinical laboratory values that were noted to be abnormal at the completion of therapy. The most common abnormal clinical laboratory parameters involved hematology tests. However, the concomitant administration of radiation and chemotherapy makes it difficult to interpret these findings. Of note, no patients are reported to have had alterations in renal function tests despite the co-administration of cisplatin in 13 patients.

6. DISCUSSION

Immediately prior to conducting this study, these investigators treated 33 head and neck cancer patients with a standard regimen of radiation or radiation plus cisplatin chemotherapy. As expected, many of these patients developed oral mucositis, including 70% of cases evaluated as being Grade 3 or 4. These investigators then conducted the herein described study. The current report is a summary of the findings in 25 head and neck cancer patients treated with the same standard regimens with the addition of MRX-1024. Table 16 and Figure 2 present the incidence and severity of oral mucositis from both populations.

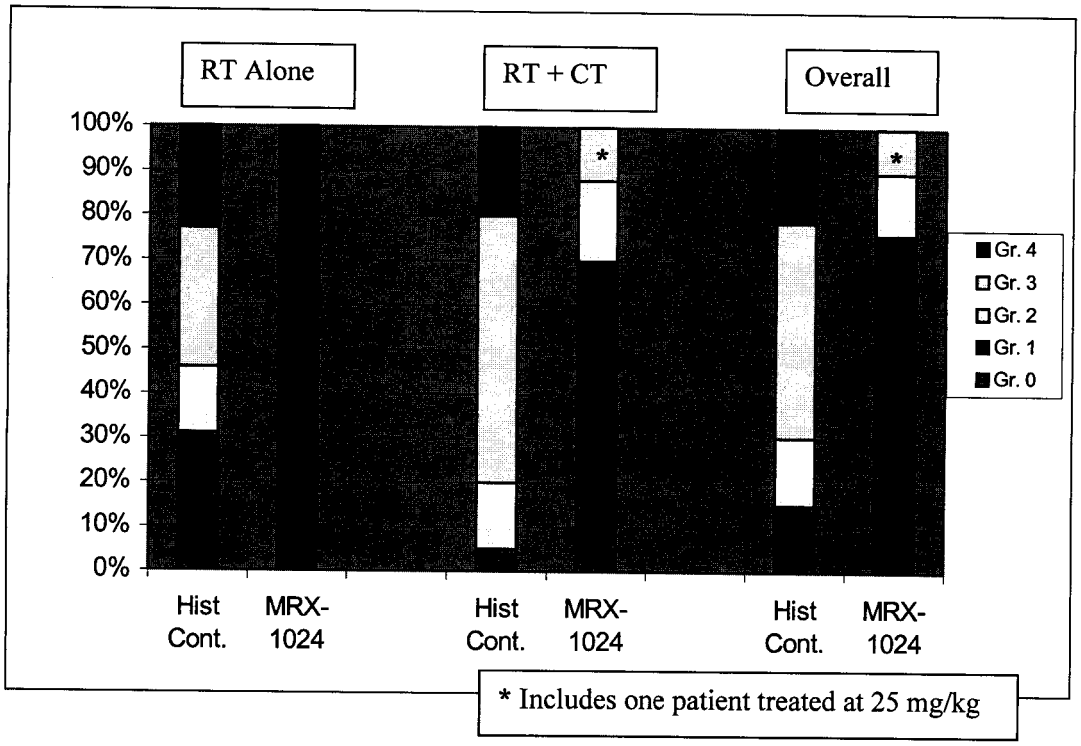
Table 16. Incidence and Severity of Oral Mucositis in Historical Control and Phase 1 Study Populations: WHO Scale

	Historical Control (N=13 for RT) (N=20 for RT+CT)					Phase 1 Study (N=4[a] for RT) (N=17[a] for RT+CT)				
	Number of Patients with Grade of Oral Mucositis					Number of Patients with Grade of Oral Mucositis				
	Gr. 0	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 0	Gr. 1	Gr. 2	Gr. 3	Gr. 4
RT	4 (31%)	0	2 (15%)	4 (31%)	3 (23%)	3 (75%)	1 (25%)	0	0	0
RT+CT	1 (5%)	0	3 (15%)	12 (60%)	4 (20%)	5 (29%)	7 (41%)	3 (18%)	2[b] (12%)	0
Overall	5 (15%)	0	5 (15%)	16 (48%)	7 (21%)	8 (38%)	8 (38%)	3 (14%)	2[b] (10%)	0

RT = Radiation Therapy
CT = Chemotherapy
[a] Two Phase 1 study patients treated with RT alone and two patients treated with RT+CT withdrew prior to the initial assessment at Visit 2 and therefore are excluded from the table.
[b] Includes one patient treated at the 25 mg/kg dose level

In contrast to the findings in the historical control group where 69% of the patients developed Grade 3 or 4 oral mucositis, only 2 patients (10%) in the Phase 1 study developed Grade 3 and no patients developed Grade 4 oral mucositis. Of note, one of these two patients was the only patient treated at the MRX-1024 dose of 25 mg/kg. All other patients received 100 mg/kg twice daily. Only 5 patients (15%) in the historical control population were spared the development of oral mucositis, whereas 8 patients (38%) in the Phase 1 study experienced no oral mucositis and an additional 8 patients (38%) had only Grade 1 toxicity. These same data are depicted in Figure 2, below.

Figure 2. Incidence and Severity of Oral Mucositis in Historical Control and Phase 1 Study Populations: WHO Scale



7. CONCLUSIONS

Definitive conclusions regarding the contribution of MRX-1024 to standard therapy await future randomized trials. On the basis of this Phase 1 study, it appears that:

- MRX-1024 is a well-tolerated agent when given orally at a dose of 100 mg/kg twice a day to patients with head and neck cancer receiving standard therapy with radiation or radiation plus cisplatin chemotherapy.
- When compared to historical control data, MRX-1024 provides a substantial protective effect against the development of oral mucositis, a common and severe consequence of radiation or radiation plus cisplatin chemotherapy, in patients with head and neck cancer.
- Antitumor activity is preserved when MRX-1024 is co-administered with radiation or radiation plus cisplatin chemotherapy to patients with head and neck cancer.

- Additional clinical trials are warranted in patients with head and neck cancer receiving standard therapy to further evaluate the contribution of MRX-1024 in reducing the incidence and severity of oral mucositis, currently a painful, debilitating and therapy-limiting consequence of treatment.

8. REFERENCES

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